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Review Article

Filing of DMF in the US, EU, and India, and its comparative review

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Abstract

A Drug Master File (DMF) covers all comprehensive, accurate, and precise information about Active Pharmaceutical Ingredient (API) or Finished Product Dosage Form (FP). It is a confidential document that contains complete, factual, and correct information about the active pharmaceutical ingredient and drug product's chemistry, manufacture, stability, purity, impurity profile, packaging, and the cGMP (Current Good Manufacturing Practices) status of any human drug product. When a DMF is filed, it allows a company to safeguard its intellectual property from its partner while complying with regulatory requirements when its process details are disclosed. There is no legalised or regulatory requirement to file a DMF. A DMF comprises of two parts: (a) the Applicant's Part (Open Part), which contains all the information to assess the quality that the license-holder requires and submit a license or amendment application; and (b) the Restricted Part (Closed Part), which contains confidential information about the manufacturing procedure which is only disclosed to the authorities.

A DMF can be used by a holder who establishes the file or by one or more parties to support their files or applications.

The present study is to brief an overview of DMF filing in different countries, which are the USA, Europe, and India. It also gives information on regulatory requirements of Drug Master Files by Food and Drug Administration (USA), European Medicines Agency (Europe), and Central Drug and Standard Control Organization (India) and their comparison.

Keywords: Drug Master File (DMF), ASMF, FDA, CDSCO, LOA, Assessment Process, MAA

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1. Introduction

A Drug Master File (DMF) is a sensitive document that contains complete, factual, and correct information about the active pharmaceutical ingredient. DMF is a document prepared by the drug products manufacturer or excipient and submitted to the targeted market's regulatory authority.

It is a submission to the FDA (Food Drug and Administration) covering information on chemistry, stability, purity, impurity profile, packaging, and cGMP status of any API. The US FDA requires a DMF submission of a drug substance, drug product, and container closure if there is an absence of relevant information in the CMC (Chemistry, Manufacturing, and Controls) section of an application, to allow FDA to review facts such as confidential details about procedures, facilities, components, or articles used in the manufacturing, processing, packaging, and storing of one or more APIs and human drugs. (1)

The information available in a DMF is used to support a New Drug Application (NDA), Investigational New Drug Application (IND), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or related documents.

The Timeline for submission of DMF is from 2-3 weeks after the main document is submitted. It should be considered that DMF's that are not submitted in the eCTD layout will be rejected by the agency. DMF holders whose DMFs are at present in paper format are not required to resubmit their entire DMFs in eCTD (Electronic Common Technical Document) format. Whether it is active or withdrawn, the status of DMF is checked on the FDA website. (2)

Note:

- If DMF is not filed, the time taken to approve the application will be 2-3 weeks
- If the DMF is admissible from an administrative point of view, the FDA issues an acknowledgment letter, which notifies the DMF number holder
- If the FDA finds the DMF not justifiable from an executive viewpoint, they inform the holder of the deficiencies and correct them

DMFs Globally

a) Highly Regulated Markets (Drug Master Files used to support the approval process)

- United States
- Canada
- Japan
- Australia
- Europe
- China is developing its own DMF system

b) Nearly Regulated Markets (Technical Package/ Registration Dossier)

- Russia
- South Africa
- Brazil

c) Less Regulated Markets (No DMFs used in the registration process)

- India and many others. (3)

2. Role of DMF

- DMF plays a crucial role for the manufacturers of Drug products and supports the documents for drug products' registration/approval.
- Registered APIs published on websites helps in the marketing of APIs to all drug product manufacturers.
- In the CMC sections of the drug submission, drugs identity, purity, strength, and quality.
- To protect proprietary and confidential information. (4)

3. Mechanism of Drug Master File

There are two stages of evaluation for DMF that go through before it is available to review its content. Initially, the FDA evaluates the inclusion of all parts of DMF in the correct order. Once DMF is determined as acceptable, it will undergo an administrative review. From an electronic technical perspective, if the DMF is not acceptable, the holder will be informed. To process the insufficient DMF to an administrative review stage, the holder must respond reasonably to any deficiency in DMF, which will be conducted by the DMF staff in the Office of Pharmaceutical Quality (OPQ). Once the DMF qualifies the administrative review and is acceptable, an Acknowledgement Letter is sent by OPQ, making it available for technical content review. Otherwise, OPQ sends an Administrative Filing Issues (AFI) letter for which the holder must respond adequately to proceed with technical content review. The time frame for this could be a couple of weeks. (5)

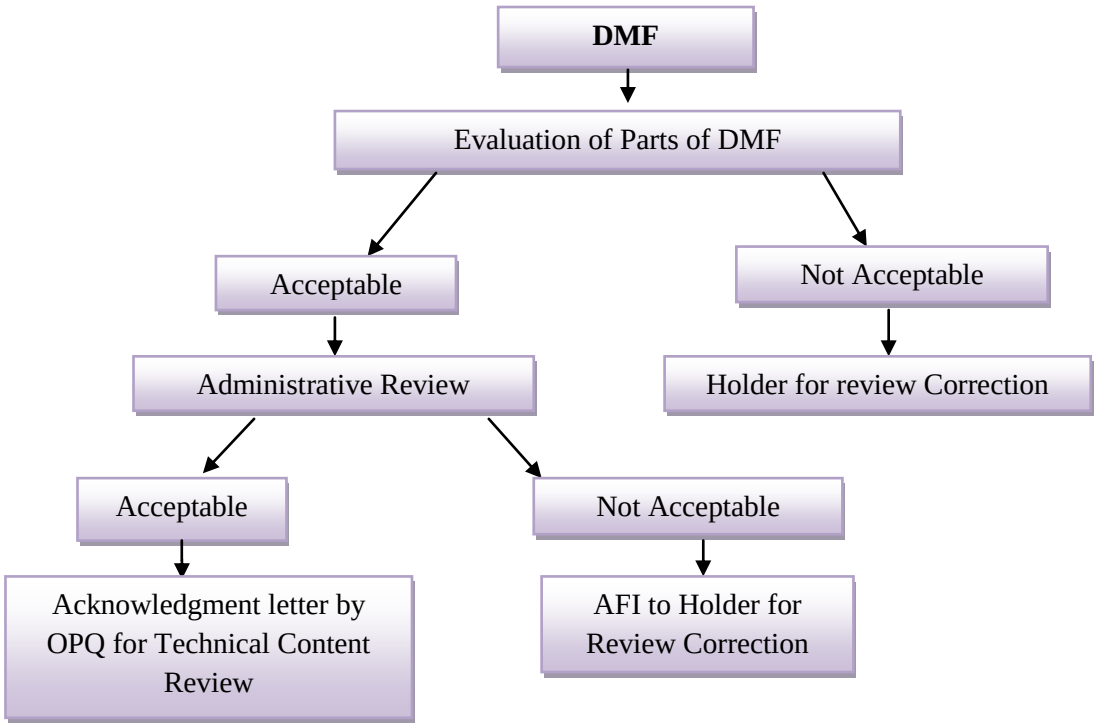

Figure 1. Flowchart for Mechanism of Drug Master File

Table 1. Differences between application and DMF

Application	DMF
1. Comes under regulatory status, which must be filed by the applicant.	1. It Does not come under regulatory status; it is not mandatory to file a DMF.
2. Each submission (supplement) is entered into the application database.	2. Each submission is entered into the database as per there types (different from the application database)
3. Submitted to a particular review division.	3. Submitted to CDR.
4. Assignment to a reviewer and an acknowledgment letter is sent.	4. No assignment to a reviewer and no acknowledgment letter is sent.
5. Each submission has a due date.	5. Has no due date

Table 2. DMF Submission types

S.NO.	Country Name	Submission Type
1.	**Europe (EDQM)**	● **MAA** (Marketing Authorization Application) - via the Centralized Procedure for eligible products and the decentralized, mutual recognition or national authorization procedure for other products
2.	**USA (USFDA)**	● **NDA** (New Drug Application) - for new drugs. ● **ANDA** (Accelerated New Drug Application)-for generics ● **BLA** (Biologic License Application) - for biologics
3.	**India (CDSCO)**	● **MAA (**Marketing Authorization Application)

4. DMF filing in the USA (US-DMF)

In the United States, the DMFs must be submitted to the FDA. The primary purpose of the DMF filing is to assist regulatory requirements and prove the quality, efficacy, safety, purity & potency of the medicinal product to apply for an IND, NDA, & an ANDA. (6) It is an elective regulatory submission and is submitted at the discretion of the DMF holder to assist their clients. A DMF is required to supply bulk Drugs to the United States but the FDA does not require all manufacturers to submit a DMF. (7)

A DMF should be neither approved nor disapproved, and a DMF is not a replacement for the IND, NDA, ANDA, or an Export Application, and it is provided in 21 CFR 314.420.

This document provides all the procedures that the firm accepts for preparing and submitting a DMF, DMF types, information required for each kind, the format of submission of a DMF, review & assessment of DMF & DMF holder obligations.

Types of Drug Master Files in the US

There are five types of DMF in the US:

Type I: – Manufacturing site, Facilities, Operating Procedures, and Personnel (no longer applicable

For a person outside of the US a Type I DMF is recommended to assist FDA in conducting onsite inspections of their manufacturing facilities.

This type contains information about manufacturing sites, facilities, operating procedures, and personnel (It is recommended for a person outside of the US to assist the FDA in conducting site inspection of their manufacturing facilities).

Type II: - Drug Substance, Drug Substance intermediate, drug product, and material used in their preparation.

Drug Substance: Summarize all significant steps in the manufacturing and controls of the drug intermediate or substance

Drug Product: Should ordinarily submit manufacturing procedures and controls for finished dosage forms in an IND, NDA, ANDA, or Export Application. If cannot submit this information in an IND, NDA, ANDA, or Export Application, it should be submitted in a DMF.

Type III: - Packaging material

Each packaging material is identified by its components, use, composition & controls for its release. Required to submit the name of the manufacturer and acceptance criteria in DMF.

Toxicological data on these materials are included under this type of DMF, otherwise available by cross-reference to another document.

Type IV: - Excipients, Flavour, Colorant, Essence, and material used in their production

Each additive is identified and characterised by its method of manufacture, testing methods, release specifications. Include toxicological data on these materials under this type of DMF.

Usually, the official compendia and FDA regulations (21 CFR) may be used as sources for release tests, specifications, and safety.

Type V: - FDA accepted reference information

Any holder wants to submit information and supporting data in a DMF not covered by Types I through IV. The reference information is used for sterile manufacturing plants and contract facilities for biotech products accepted by the Food Drug and Administration.

The Type 2, 3& 4 DMF should contain guarantees by the firm that all of its facilities are operating according to the applicable laws. FDA discourages the usage of Type V DMF's for miscellaneous information, duplicate

information, or information which is included in one of the other types of DMF's. (8)

DMF Submission

Each DMF submission should contain a transmittal letter, administrative information, and the specific information involved in the DMF.

The DMF should be in the English language. Whenever a submission contains information in another language, an accurate certified English translation should be also included. (9)

Each page of each copy of the DMF should be dated and consecutively numbered and should include an updated table of contents with each submission. For each submission covering letter should be prepared to facilitate the processing of documents; list the submission type in bold type in the cover letter's header.

All submissions should be made through Electronic Submissions Gateway in e-CTD format. The DMF should be compiled in an e-CTD format as per the US FDA guidance. The documents scanned/ converted should be legible and searchable.

Transmittal Letters

The following should be included:

Original submissions

A. Identification of submission

B. Identification of the applications that the DMF is intended to support, including the name and address of each applicant, sponsor, holder, and all the relevant document numbers.

C. Signature of the authorised representative or the holder.

D. Typewritten name and title of the signer.

Amendments

A. Name of DMF holder.

B. DMF number.

C. Name and address for correspondence.

D. Page numbers and Affected section and of DMF.

E. The name and address of each person whose NDA, IND, ANDA, or export application relies on the subject of the amendment for support.

F. The number of each NDA, IND, ANDA, DMF, and export application that relies on the subject of the amendment for support, if known.

G. Particular items within the NDA, IND, ANDA, DMF, and export application that are affected if known.

Administrative information

Administrative information should include the following:

A. Names and addresses of the following:

- DMF holder.
- Manufacturing/processing facility.
- Corporate headquarters.
- Contact for FDA correspondence.
- Agent(s).

B. The particular responsibilities of each person listed in any of the categories in section a.

C. Statement of commitment.

A Signed statement by the holder certifies that the DMF is current and that the DMF holder will comply with its statements.

Font, font size, format & paper used for submission to USFDA

- DMF must be filed in electronic format only.
- In CTD, the information should be clear to facilitate the review of the basic data.
- US standard paper size (8.5 by 11 inches) is preferred.
- Text and tables should be prepared using margins to be printed on an A4 sheet.
- Times new roman, 12-point font is recommended for narrative text. Every page should be numbered.
- Paper length should not be less than 10 inches nor more than 12 inches.

Letter of Authorization to FDA

The DMF will be reviewed only when it is referenced in another DMF or in an application. The holder should submit an LOA (2 copies) to the DMF and do not neglect this. Then send a copy to the applicant. The applicant submits a copy of the LOA in their application. It is only a mechanism to trigger a review of the DMF.

In some cases, a DMF holder will call the permission to reference a DMF a "letter of access." An LOA does not permit anyone except FDA to "access," i.e., "Read" the DMF and must contain a specific reference to a particular item in the DMF. It is essential for large type III or IV DMFs that have many products.

Specify the item by its code name, page number, and, most importantly, date of submission. It appears on the cover letter of that submission (not an internal document date) volume numbers usually not helpful since volume numbers are generated in CDR.

The letter of authorization should include the following:

- Name of DMF holder
- The date
- Name of person(s) authorised to incorporate the information in the DMF by reference
- DMF number
- The specific product(s) covered by the DMF
- Submission date(s)

- Page numbers and Section numbers and to be referenced
- Statement of commitment that the DMF is current and that the DMF holder will comply with its statements
- Signature of authorizing official
- Typed name and title of official authorizing reference to the DMF

DMF Filing Process

Two copies of the DMF with one signed original of the covering letter, and other necessary documents are sent to the FDA's Central Drug Evaluation and Research (CDRL).

The DMF staff will audit the non-technical information for adequacy and completeness for submission. If the key elements are missing, the staff will contact the proposed holder to obtain the necessary documents to file the DMF.

Once the DMFs are determined to be acceptable for filing, the document room staff assigns a DMF number, and a letter is sent to the contact person listed in the DMF.

Holder obligations

Any change or addition in DMF or authorization related to specific customers should be submitted in duplicate copy and with reference to the previous submission. The reference should include the date, section, volume, and or page number affected. (10)

A DMF should contain a record of persons authorised to incorporate the DMF information by reference (21 CFR 314.420). The DMF holder should update the list yearly.

It should contain the holder's name, DMF number &date of the update. If any person's authorization is withdrawn during the previous year, it should be identified under a suitable & different caption.

Transfer of ownership

If the DMF holder wants to grant DMF ownership to any other person, the holder should inform the FDA and authorised person about giving ownership in writing. (11)

The letter should include:

a. Name of the transferee

b. Address of transferee

c. Name of a responsible official of the transferee

d. Effective date of transferee

e. Sign of transferee

The new holder should submit a letter of acceptance of DMF ownership & have to update all the DMF information and any new ownership changes.

Closure of a DMF

A holder who wants to close a DMF should submit a request to the DMF staff stating the reason for the closure.

The agency may close a DMF that does not contain an annual update of persons authorised to incorporate the DMF information and a list of changes made since the previous annual report. The holder will be notified of the FDA'S intent to close the DMF.

Reactivating a closed DMF:

The holder must submit a complete copy of the DMF and a reactivation request, including revisions since the last submissions, once the reactivation request enters into DARRTS. The status of DMF changes to 'ACTIVE'

DARRTS – Document archiving reporting and regulatory tracking; it is an archival system of record for all new and subsequent INDs, NDAs, ANDAs, DMFs, BLAs.

5. DMF filing in EU

European DMF was established in 1989-1991 and was revised in 2005. It became Active Substance Master File (ASMF) after the implementation of CTD in the EU. The ASMF in Europe is covered under Directive 2001/83/EC. The content & format in the US and EU is different. The application of the ASMF, commonly known as the European drug master file (EDMF), is to secure the intellectual property and at the same time allow the applicant to take full responsibility for quality control of the active substance and medicinal product. (12)

The EDMF is a document containing the information required to demonstrate that the quality of the active ingredient is adequately controlled by the specification proposed by the applicant, which must collaborate with the company submitting a separate EDMF to ensure that all relevant information is required is supplied. (13)

The content and the format for DMF used in the US differ from those of European Countries to obtain Marketing Authorization. (14)

The entire information essential for the suitability assessment of the active ingredient in the pharmaceutical products shall be approved by EMEA or the appropriate authorities. The eCTD format has become mandated by the centralized protocol for submissions of human ASMFs, since 1 July 2016. EU Directive 2003/63/EC defines the list of the active substance for which ASMF can be submitted which include information –

a. Full description of the manufacturing process

b. Quality control procedure during manufacture

c. Process validation

Objective

a. To support the regulatory requirements of a medicinal product to prove its quality, safety, and efficacy.

b. To help obtain Marketing Authorization grant. (15)

Market Authorization Application (MAA)

Before submitting MAA, the applicant should notify the EMEA (European medicine agency) about their intention to submit an application & submit an estimated month of submission.

MAA can be filled in four different ways:

a) National Procedure: The national procedure is preferred if an organization wants only one EU country to market their product. The organization must inform the relevant authority before filing for MAA. The organization must submit an application to the competent authority of the member states for obtaining national MAA. Applications for market authorization must be completed within 210 days.

b) Centralized Procedure: In this marketing authorization is granted for the entire community market that is valid in the all-member states' market. The regulation (EC) 726/2004 lies down a centralized procedure for medicinal products authorization. For this, there is a single application, a single procedure for evaluation & a single authorization allowing direct entry to the community's single market.

c) Mutual Recognition Procedure: This procedure is preferred; if a company has market authorization in one of the EU member states and wants to get approval in several countries can simultaneously apply for this to get recognised in other EU countries. It is a quicker way to reach the market.

d) Decentralized Procedure: This procedure is preferred if products do not come under EMA's scope in the centralized procedure. In this procedure, the company can apply for simultaneous authorization in more than one EU country for products that are not yet authorised in any EU countries.

Content of the ASMF

The EDMF should include all the details related to scientific information for medicinal products market authorization in the EU member states. (16)

EDMF for human medicinal products should be represented in the form of a common technical document (CTD).

EDMFs for veterinary medicinal products must also be presented in CTD form after the consultation with Competent Authorities/EMEA. EDMF linked to a veterinary medicinal product should include:

- Name and site of active substance manufacturer
- Nomenclature
- Description
- Outline of the manufacturing route
- A detailed description of a manufacturing method
- Quality control during manufacture
- Development chemistry
- Analytical validation
- Impurities
- Batch analysis
- Stability studies

In the EDMF the scientific information should be divided into separate parts, namely the **Applicants Part (AP)** and the **Restricted Part (RP).** (16)

a) **Applicant's Part:** It is open and contains information that is not confidential to the applicant. It should include sufficient information so that the applicant can take full responsibility for evaluating suitability for the active substance used in manufacturing a specified medicinal product. Can consider the applicant part as confidential because cannot submit it to the third parties without the EDMF holder's written consent.

b) **Restricted Part:** It is closed, contains the information which is considered confidential, and includes all the information such as detailed information about individual steps of manufacturing methods like reaction conditions, temperature, validation data of critical steps.

When the EDMF is provided in CTD format, it should provide both summaries in Quality Overall Summary Type. Both applicants and restricted parts should have a version number, which should be unique and follow a logical order.

European DMF Filing Procedure

The API manufacturer provides the applicant's part DMF to the applicant, which contains both the applicant & restricted part. Then it becomes part of the MAA, and it is further submitted to the authorities.

The purpose of the ASMF is to maintain confidentiality and protect the information about the active substance. It also allows the applicant to take full responsibility for the medicinal product's quality, safety & efficacy. National competent authorities then assess the complete information necessary to check the suitability of active substances in medicinal products.

For the following active substances, the ASMF procedure is used (expect active biological substances):

- New active substance
- The existing active substance that is not included in European pharmacopeia
- Pharmacopoeia active substance that is included in European pharmacopeia
- The ASMF procedure cannot be used for biologically active substances

The EDMF holder should submit to the MA holder/applicant:

- A copy of the latest version of the applicant's part
- A copy of the Quality Overall Summary (QOS) on the latest version of the applicant's part
- A copy of LOA where the letter has not been submitted earlier for the product concerned

- For each MAA or each MAV (market authorization variation), the EDMF holder should submit the EDMF to the competent authorities

Changes & Updates to the ASMF

For all medicinal products, the EDMF holders should keep the content of their EDMFs updated according to the actual synthesis or manufacturing process. (14) EDMF holders should not change the contents of the EDMF without the written consent of the applicant and competent authority. Before making any change in EDMF, EMEA, the applicant should be informed.

Should mention all the changes in a covering letter. The covering letter to the EMEA should contain the following information:

- A summary of all the changes carried out since first submission of the
- EDMF
- Information regarding whether the change has been accepted, rejected, or withdrawn by other member states
- An updated quality overall summary

A collation between old and new contents of EDMF

- The new applicant's part / restricted part with each a new version number

Assessment Process for DMFs (27066-Article text)

Based on the DMFs' relationship to a related drug product assessment process, DMF assessment processes can be classified as follows:

A. Group 1 (assessment process is in conjunction with a drug product assessment process)

B. Group 2 (assessment process is independent of a drug product assessment process)

The Group 1 organizations undertake the DMF assessment process in conjunction with the drug product assessment process (i.e., the DMF has been referenced in an application for a drug product). The drug product applicant, the DMF holder, and the regulatory agency are involved in the DMF assessment process. All organizations in Group 1 adopt the Applicant's Part/Restricted Part structure. By adopting this structure, a regulatory agency can discuss the non-proprietary information in the Applicant's Part because the Applicant's Part is itself shared with the applicant.

The Group 2 organizations undertake the ASMF/DMF assessment process independent of the drug product assessment process. All assessment processes are completed between the ASMF/DMF holder or in-country caretaker and the regulatory agency. (17)

6. Drug Master Filing in India

There are no drug master file guidelines issued by the Indian regulatory authorities Central Drug Standard Control Organization (CDSCO). In India, generally United States' DMF format is used to submit confidential information to drug substances and drug products to regulatory authorities. A DMF may be filed for a bulk drug and formulation. A DMF declared by the company provides in detail the manufacturing place, physiochemical properties, toxicological studies of bulk drug and formulation, Pharmacodynamic /kinetic, therapeutic classes, dosage form, strength, route of administration, Labelling and packaging, etc. (17) Suppose any foreign manufacturer wants to be obtained a drug marketing license in India for a drug product manufactured in a foreign country. In such a case, the manufacturer should submit all chemistry manufacturing and controls (CMSs) information on drug products in Indian CTD format to CDSCO. If foreign drug products, drug substances, intermediates, etc. accepted DMF by USFDA, Europe or any other country should be submitted and the application for approval of India's drug products. India continues to lead in the number of DMF filed with the USFDA. (18)

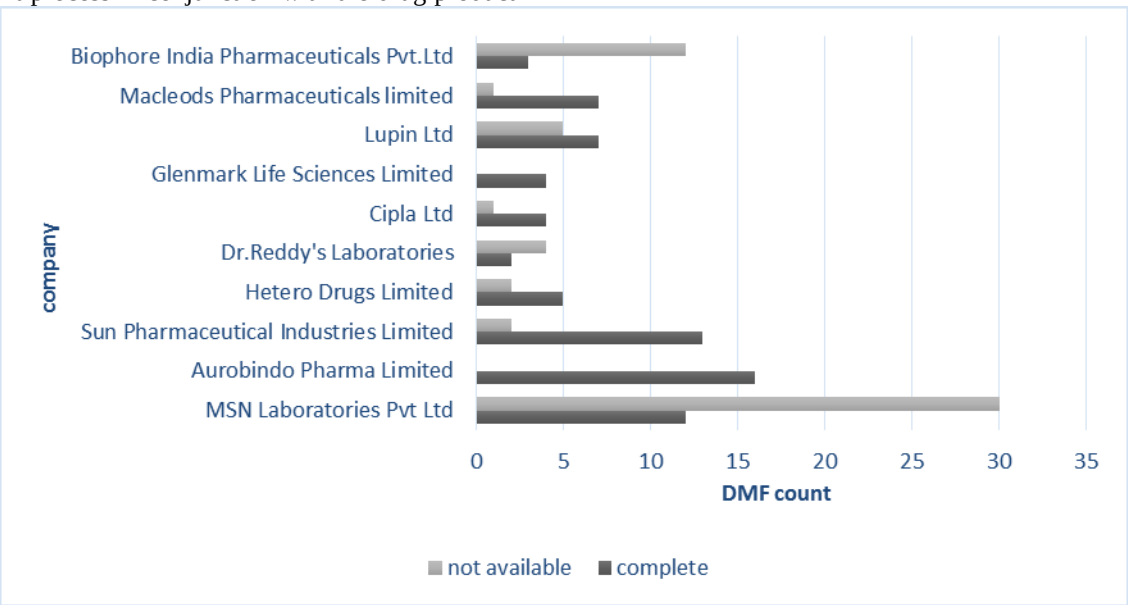

Figure 2. DMF Filings by Indian companies in 2019 (19)

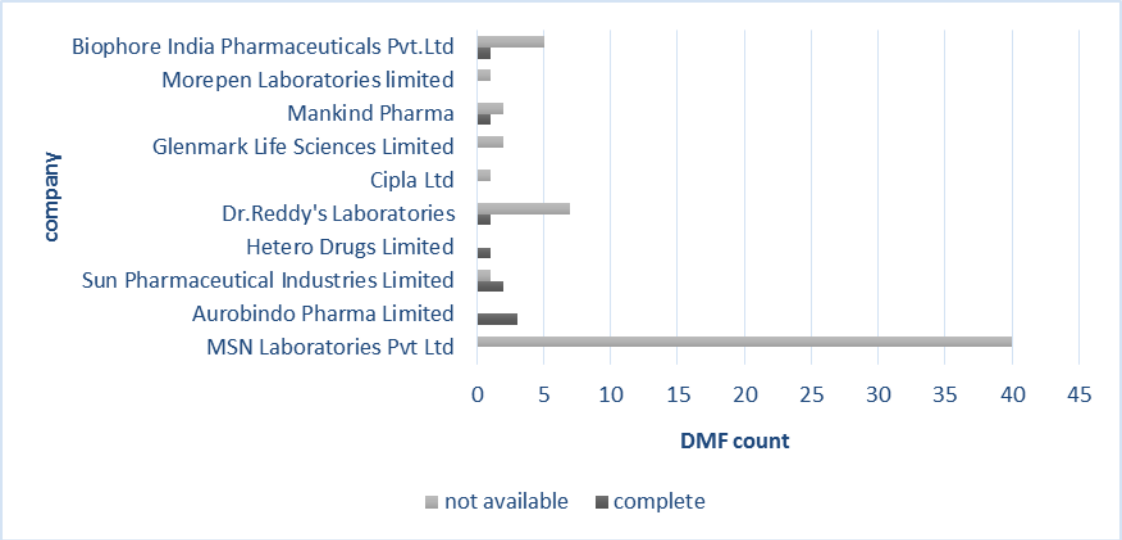

Figure 3. DMF count by Indian companies till June 2020 (20)

The above figure indicates company-wise DMF filings for Indian companies in the year 2019. MSN Labs continued to lead the count of total DMF filings with 42, of which it had 17 filings where it was the only one submitting a DMF for a specific product in 2019. The other Major Indian generic drug companies like Aurobindo (16), Sun Pharmaceuticals (13), hetero (5), Cipla (4), and Macleods (7) Led, the list of companies that had the maximum DMF assessments completed for their 2019 submissions. The year 2019 witnessed continued DMF filings for Rivaroxaban, Sitagliptin Phosphate, Ticagrelor, and Tipiracil Hydrochloride. These filings indicate that the companies currently developing these products should brace themselves for intense competition in the near future.

Figure 3 signifies company-wise DMF filings for Indian companies till June 2020. As in the past, India's MSN Laboratories continued to lead the DMF filings by a single company with 40 submissions, followed by Dr. Reddy's (8). MSN has always been a pioneer in being the first to file a DMF for new products. This year was no different. The firm submitted the first DMF for 11 products - Abaloparatide, Abemaciclib, Amifampridine Phosphate, Betrixaban Maleate, Fenfluramine Hydrochloride, Lofexidine Hydrochloride, Neratinib Maleate, Ozenoxacin, Rolapitant Hydrochloride, Tafamidis, Valbenazine Tosylate.

7. Comparison of Drug Master Filing in the US, EU, India

Table 3. The comparative study of DMFs between the US, EU, and India (17)

S.no.	Parameters	US	EU	India
1.	Regulatory Authority	Food and Drug Administration (FDA)	CEP: European Directorate for Quality of Medicines and Healthcare (EDQM) ASMF: European Medicines Agency (EMA)	Central Drug and Standard Control Organization (CDSCO)
2.	Use of DMF in Support of Application	IND, NDA, ANDA	MAA	MAA
3.	Mandatory	No	No	No
4.	Information Provided	Drug Substance Intermediate, Drug Products, Flavours Etc.	Active Substance	API, Drug Products, Flavours, Colorants, Etc.
5.	Fees for Assessment	Only for ANDA	No Fee	No Fee
6.	Submission in CTD Format	Required	Required	Required in Indian CTD format.
7.	Forms for DMF Filling	Not Applicable Except Type I DMF, Form FDA 3794	Not Applicable	Not Applicable
8.	Language	English	English	English
9.	Submission of DMF	eCTD format	eCTD format	eCTD format
10.	DMF Number Assigned by Reviewers	Yes	No	No

11.	Approved/Disapproved by Regulatory Authority	Not Approved and Only Accepted in Support of Applications	Only Accepted	Only Accepted
12.	Deficiency Letter	Applicable	Applicable	Applicable
13.	Changes and Approved	Applicable	Applicable	Applicable
14.	Appointment of In-Country Care Taker	Applicable	Applicable	Applicable
15.	Letter of Authorization	Applicable	Applicable	Applicable
16.	Closure or Withdrawal	Applicable	Applicable	Applicable
17.	Reactivation	Applicable	Applicable	Applicable

8. DMFs count by countries in 2019 and 2020

In the first six months of the year 2019, the FDA received 283 DMF submissions (against 616 for the full year of 2019). Expectedly, India continued to lead with 155 DMF filings. Submissions from India were more than double the amount of those made by Chinese (45) and American firms (30) combined. Figure (Fig: 3) shows India, the US, and the EU's DMF filings till June 2020.

This trend has been witnessed for some time now. In 2019, out of the 616 active DMF submissions to the FDA, Indian companies had submitted more than half (331), though the submissions from India were a little less than double of those made by Chinese (113) and American (57) firms. Figure (Fig: 4) shows India's DMF filings, US and EU for the year 2019.

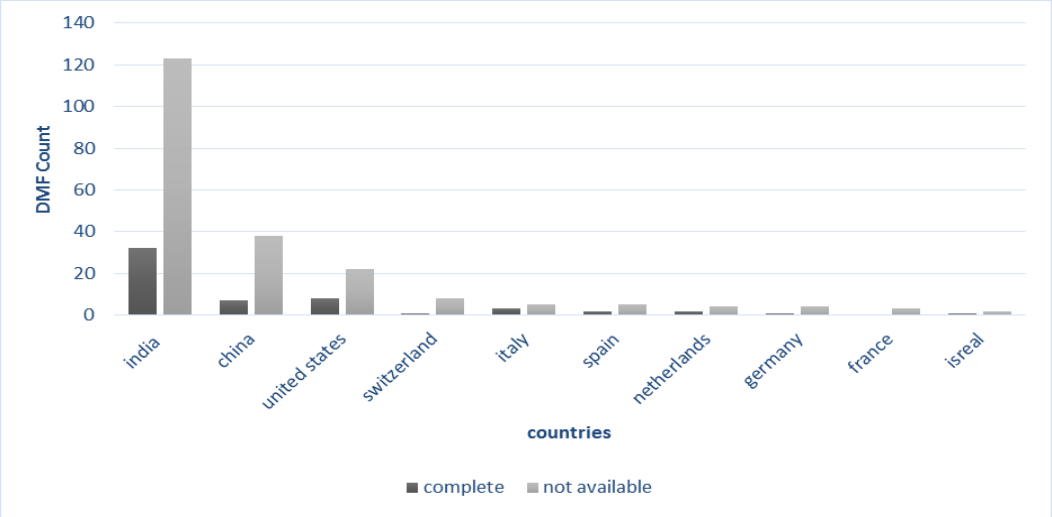

Figure 4. DMF count by countries till June 2020 (20)

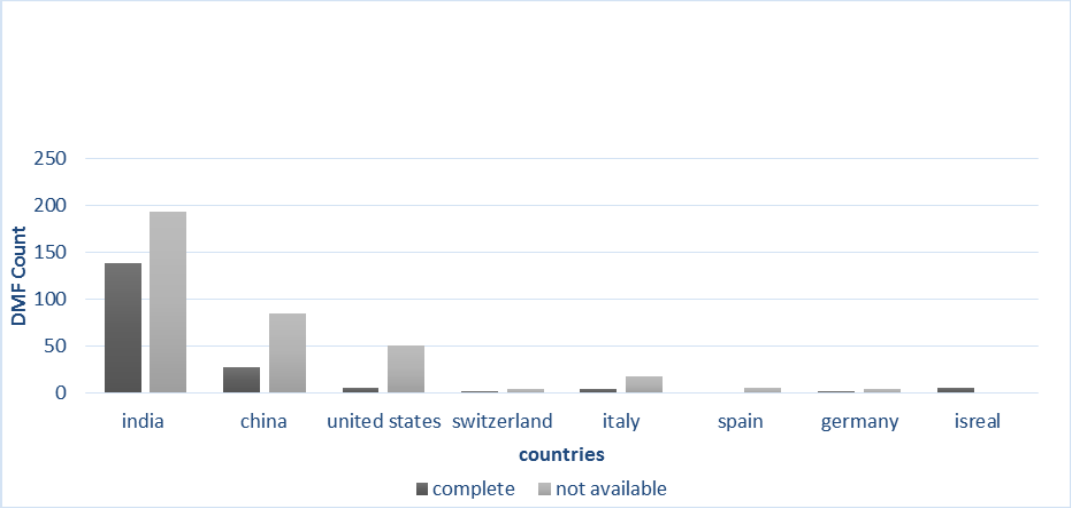

Figure 5. DMF count by countries in 2019 (19)

Benefits of DMF services (21)

- Gives an edge over the competitors
- Ensures confidentiality of proprietary information
- Several applicants can refer to the information
- It will add status to the company and the product
- Establish a good rapport with customers
- Improve sales globally
- It will penetrate the high entry barrier in the US market

9. Case Studies

A. An Indian pharmaceutical company (the name is confidential) develops, manufactures, and markets a broad range of pharmaceutical products and various in-house products. They lacked a centralized repository for information and could not monitor the progress of various processes. The drug information was shared with regulatory and marketing stakeholders, which is not appropriately protected. They also lacked insight into the existing data; gaining access to this information was also a huge problem.

A DMF helps in keeping the drug information confidential and protect it. Hence, the company must register in the DMF and overcome this issue. (22)

B. A pharmaceutical company in India (the name is confidential) had a loss in sales compared to its competitors. To detect the problem, assessed all the concerned pharmaceutical companies for their reputation and technical capabilities. It was then revealed that most of the leading companies had US DMF for their products.

Can overcome it by implementing cGMP training and filing US DMF. It results in vastly improved sales enquiries and actual orders. (23)

C. The applicability of sucrose laurate as a surfactant in solid dispersions is studied. The US DMF already contains sucrose laurate, but it is never used as a surfactant. It will lead to a delay in its usage and confirm its consistency in various formulations.

It can be overcome by a clear and detailed study of the surfactant, whether mentioned in any of the country's DMF or not and performing the studies. (24)

D. A multinational chemical company (the name is confidential) was lacking internal expertise during workload peaks and was not able to protect its DMFs. They decided to convert all existing DMFs into eCTD format (eCTD submissions for global DMF portfolio). Therefore, they took assistance from regulatory authorities, which offered support with eCTD publishing, electronic submission for DMF maintenance activities, and consultancy for electronic submission management. Performed the dossier compilation, publishing, and validation.

This helped in developing full access to a pool of eCTD and electronic submission experts and flexible handling of the workload peaks. (25)

10. Conclusion

The paper indicates that the drug master file is filed in aid of various customer applications. There is no obligation in either country to register the drug master file. There are numerous rules and regulations for each nation of the world to file a drug master file (DMF). So, there is a need to harmonize the world's DMF filling. It is necessary to register in a DMF, considering its role and benefits, in order to protect the information like active ingredients, procedure, and processes used for developing a novel drug product. The content and the format for the Drug Master File is used to obtain Marketing Authorization. The main objective of the DMF is to support regulatory requirements of a medicinal product to prove its quality, safety, and efficacy. It helps to obtain a marketing authorization grant.

India must develop its own format for filing a DMF, instead of following other countries, US, DMF format. Now onwards, most of the nations will use the eCTD format for DMF submission.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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